Germ-layer and lineage-restricted stem/progenitors regenerate the mouse digit tip.

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Public Summary:
The regrowth of amputated limbs and the distal tips of digits represent models of tissue regeneration in amphibians, fish, and mice. For decades it had been assumed that during limb regeneration, the same population of cells, located within a growth zone called 'blastema' gives rise to all of the different tissues that are regrown. Here we show that distinct tissue stem/progenitor cells contribute to restore the mouse distal digit tissues. Genetic fate mapping of the different tissues within the digit and clonal analysis of individual cells revealed that these stem cells are lineage restricted, mimicking digit growth during development. Transplantation of CFP expressing hematopoietic stem cells, and parabiosis between genetically marked mice, confirmed that the stem/progenitors are tissue resident, including the cells involved in angiogenesis. These results, combined with those from appendage development/regeneration in lower vertebrates, collectively demonstrate that tissue stem cells rather than pluripotent blastema cells are an evolutionarily conserved cellular mode for limb regeneration after amputation.

Scientific Abstract:
The regrowth of amputated limbs and the distal tips of digits represent models of tissue regeneration in amphibians, fish and mice. For decades it had been assumed that limb regeneration derived from the blastema, an undifferentiated pluripotent cell population thought to be derived from mature cells via dedifferentiation. Here we show that a wide range of tissue stem/progenitor cells contribute towards the restoration of the mouse distal digit. Genetic fate mapping and clonal analysis of individual cells revealed that these stem cells are lineage restricted, mimicking digit growth during development. Transplantation of cyan-fluorescent-protein-expressing haematopoietic stem cells, and parabiosis between genetically marked mice, confirmed that the stem/progenitor cells are tissue resident, including the cells involved in angiogenesis. These results, combined with those from appendage regeneration in other vertebrate subphyla, collectively demonstrate that tissue stem cells rather than pluripotent blastema cells are an evolutionarily conserved cellular mode for limb regeneration after amputation.